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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/996,484	**Applicant(s)** CHOO ET AL.	
	Examiner JENNIFER DUNSTON	**Art Unit** 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 04 August 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See continuation sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *34 and 48*.
   Claim(s) withdrawn from consideration: *1,2,4,5,7,8,10,11,13-15,21-26,31,34,35 and 38-48*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See continuation sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Jennifer Dunston, Ph.D.
Examiner
Art Unit: 1636

CONTINUATION SHEET

Applicant's arguments, see pages 2-5, filed 8/4/2008, with respect to the rejection of claims 34 and 48 under 35 U.S.C. 112, first paragraph, have been fully considered and are persuasive. The previous rejection of claims 34 and 48 has been withdrawn.

Applicant's arguments, see page 5-6, filed 8/4/2008, with respect to the rejection of claims 34 and 48 under 35 U.S.C. 112, second paragraph, have been fully considered and are persuasive. The previous rejection of claims 34 and 48 has been withdrawn.

With respect to the rejection of claims 34 and 48 under 35 U.S.C. 103(a) as being unpatentable over Gilman et al (WO 96/06110), Applicant's arguments filed 8/4/2008 have been fully considered but they are not persuasive.

Claim 34 is directed to a complex comprising a heterodimer comprising a first and second polypeptide, wherein the first and second polypeptides bind to DNA and the first or second polypeptide comprises an engineered, non-naturally occurring Cys2-His2 zinc finger binding domain, and a ligand that binds to the first and second polypeptides and mediates heterodimerization of the first and second polypeptides.

Claim 48 is directed to a switching system comprising a first and second polypeptide and a ligand in which the first polypeptide binds to the second polypeptide to form a heterodimer and the binding of the first and second polypeptides is mediated by binding the ligand to the first and second polypeptides, wherein the first and second polypeptides bind to DNA and the first or second polypeptide comprises an engineered Cys2-His2 zinc finger DNA binding domain.

The specification defines the term "a non-naturally occurring binding domain" to mean that "the binding domain does not occur in nature, even as part of a larger molecule, and has

been obtained by deliberate mutagenesis procedures or *de novo* design techniques." See page 3, lines 29-32.

The response asserts that Gilman fails to teach or suggest anything about engineered zinc finger proteins in addition to failing to teach anything about non-naturally occurring Cys2-His2 zinc finger binding domains.

This argument is not found persuasive. Gilman et al teach that suitable component DNA binding domains include naturally occurring zinc fingers of the C2H2 (i.e., Cys2-His2) class (e.g., page 5, lines 14-16 and 27-35). However, the teachings of Gilman et al are not limited to naturally occurring Cys2-His2 zinc finger domains. Gilman et al teach that an existing Cys2-His2 DNA binding domain can be modified, or engineered, to decrease, increase or change the recognition specificity of DNA binding (e.g., page 10, lines 4-6). Specifically, Gilman et al teach that in zinc fingers, substitutions can be made at selected positions in the DNA recognition helix (e.g., page 10, lines 11-13). Thus, Gilman et al teach the application of deliberate mutagenesis procedures to create a non-naturally occurring zinc finger sequence that has been designed to bind a particular target sequence (e.g., page 1, lines 12-15; page 10, lines 4-15). The mutagenized naturally occurring zinc finger of Gilman et al is consistent with the definition of "non-naturally occurring" provided in the instant specification. Accordingly, Gilman et al do teach engineered zinc finger proteins that are non-naturally occurring Cys2-His2 zinc finger binding domains.

The response asserts that Gilman fails to teach, suggest or enable complexes as claimed in which heterodimerization of first and second DNA binding domains is mediated by a ligand

that binds to the DNA binding domains. The response notes that Gilman teaches fusion proteins comprising a DNA binding domain and immunophilin ligand-binding domain.

These arguments are not found persuasive. The instant claims do not require the ligand to bind directly to the DNA binding domain as suggested by Applicant. Rather, the claims only require the ligand to bind the first polypeptide and second polypeptide, where each polypeptide comprises a DNA binding domain. The claims do not prohibit the inclusion of a second domain in each polypeptide where the additional domain binds the ligand. Thus, the DNA binding domain and immunophilin ligand-binding domain fusions of Gilman et al read on the first and second polypeptide of the rejected claims.

The response notes that Gilman teaches the covalent linkage of DNA binding domains. Further, the response notes that Gilman only exemplifies DNA binding domains that have been covalently linked. The response asserts that Gilman does not teach or suggest the claimed complexes in which the ligand mediates heterodimerization by binding to the DNA-binding polypeptide.

These arguments are not found persuasive. Although Gilman et al do teach the covalent linkage of DNA binding domains, the reference is available as prior art for all that it teaches. At the paragraph bridging pages 2-3, Gilman et al state the following:

> It bears repeating, and should be kept in mind by the reader, that the composite DNA binding protein in certain embodiments is a single chimeric protein containing multiple and covalently-linked copies of one or more DNA-binding domains, while in other embodiments the composite DNA-binding protein comprises two (or more) "subunits", each of which is a chimeric protein in its own right containing at least one DNA-binding domain. In the latter case, the composite DNA-binding protein comprises two or more such subunits in a multimerizer-mediated association.

Thus, it is clear that Gilman et al teach two polypeptide subunits, where each subunit comprises a DNA binding domain, and the DNA binding domains are brought together by a ligand in what Gilman et al call multimerizer-mediated association. Gilman et al teach the multimerization of at least two chimeric proteins, each comprising at least one binding site for a multimerizing ligand, and at least one component DNA binding domain, such as a modified Cys2-His2 zinc finger, where the DNA binding domains are brought together in a complex by the ligand (e.g., page 5, lines 4-12; page 7, lines 29-31; sentence bridging pages 7-8). Gilman state, "the transcriptional activation domain may be present on a chimeric protein which further contains one or more component DNA-binding domains, which is capable of dimerizing, in the presence of a dimerizing agent, with another chimeric protein of this invention bearing a ligand-binding domain and one or more additional component DNA-binding domains." Furthermore, Gilman et al teach that the design of chimeric proteins comprising ligand binding sites capable of ligand-mediated multimerization was known in the art (e.g., page 5, lines 8-12; page 8, lines 9-19). Thus, Gilman et al do teach the claimed complexes in which the ligand mediates heterodimerization by binding to the polypeptide comprising the DNA binding domain as claimed.

The response asserts that the Gilman reference does not place the public in possession of ligand-mediated heterodimeric complexes as claimed. The response asserts that Gilman only discloses covalent linkage of DNA binding domains; however, Gilman teaches the ligand-mediated association of DNA binding domains in addition to covalent association. See the discussion above.

Gilman et al teach each element of the claimed invention and placed the public in possession of the presently claimed invention. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
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/JD/

/ Christopher S. F. Low /
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